

[0007] Thus, provided in certain aspectexamples are **CD137 Binding Molecules**, such as monospecific antibodies, and molecules comprising epitope-binding fragments thereof, that are capable of binding to an epitope of CD137. The inventiondisclosure is further directed to multispecific **CD137 Binding Molecules** (e.g., bispecific antibodies, bispecific diabodies, BiTEs, trivalent binding molecules, etc.) that are capable of binding to both an epitope of CD137 and to an epitope of a second antigen, particularly a tumor antigen (“TA”) (e.g., a “**CD137 x TA Binding Molecule**”). The inventiondisclosure also provides novel **PD-L1 Binding Molecules**, such as monospecific antibodies, and molecules comprising epitope-binding fragments thereof, that are capable of binding to an epitope of PD-L1, as well as derivatives thereof and uses thereof. The present inventiondisclosure is also directed to pharmaceutical compositions that comprise such molecules. The inventiondisclosure also includes the use of such molecules in the treatment of disease, especially cancer or a disease or condition associated with or characterized by the presence of a suppressed immune system.

[0008] The present inventiondisclosure provides novel **CD137 Binding Molecules** that exhibit desirable characteristics particularly when incorporated into multispecific molecules. The present inventiondisclosure is also directed to multispecific **CD137 x TA Binding Molecules** that are composed of polypeptide chains that associate with one another to form two binding sites each specific for an epitope of CD137 and two binding sites each specific for an epitope of a TA. Such **CD137 x TA Binding Molecules** of the inventiondisclosure are termed “**bispecific tetravalent.**” The present inventiondisclosure is also directed to **CD137 x TA Binding Molecules** that are composed of polypeptide chains that associate with one another to form two binding sites each specific for an epitope of CD137 and one binding site specific for an epitope of a TA. Such **CD137 x TA Binding Molecules** of the inventiondisclosure are termed “**bispecific trivalent.**” The binding molecules of the inventiondisclosure (e.g., **CD137 Binding Molecules**) sometimes include a first binding site without including a second binding site that immunospecifically binds to an antigen different than the antigen to which the first binding site binds. The binding molecules of the inventiondisclosure therefore sometimes include only a first binding site, and a first Light Chain Variable Domain and a first Heavy Chain Variable Domain, and not a second binding site, second Light Chain Variable Domain or second Heavy Chain Variable Domain that bind to a different antigen than the first binding site, and non-limiting examples of such binding molecules include scFv, antibody and Fab binding molecules.

[0009] The present inventiondisclosure provides **CD137 x TA Binding Molecules** that comprise four polypeptide chains (a “first,” “second,” “third,” and “fourth” polypeptide chain), wherein

the first and second polypeptide chains are covalently bonded to one another, the third and fourth polypeptide chains are covalently bonded to one another, and the first and third polypeptide chains are covalently bonded to one another. Also provided are **CD137 x TA Binding Molecules** of the ~~invention~~disclosure comprising five polypeptide chains (a “first,” “second,” “third,” “fourth,” and “fifth” polypeptide chain), wherein the first and second polypeptide chains are covalently bonded to one another, the third and fourth polypeptide chain are covalently bonded to one another, the third and fifth polypeptide chains are covalently bonded to one another, and the first and third polypeptide chains are covalently bonded to one another.

[0010] In ~~one aspect~~detail, the ~~present disclosure refers to invention~~provides a **CD137 Binding Molecule** comprising a first binding site that immunospecifically binds to an epitope of CD137, wherein ~~said~~the first binding site comprises a first Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a first Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; and wherein:

- (A) ~~said~~the first Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **CD137 MAB-6 VL1 (SEQ ID NO:50)**; and
- (B) ~~said~~the first Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **CD137 MAB-6 VH1 (SEQ ID NO:46)**.

[0011] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1 (SEQ ID NO:46)**.

[0012] The ~~invention~~disclosure further concerns the ~~embodiment~~examples of such a **CD137 Binding Molecule**, wherein the first Light Chain Variable Domain comprises the amino acid sequence of:

- (A) **hCD137 MAB-6 VL_x (SEQ ID NO:54)**;
- (B) **hCD137 MAB-6 VL1 (SEQ ID NO:50)**;
- (B) **hCD137 MAB-6 VL2 (SEQ ID NO:55)**; or
- (C) **hCD137 MAB-6 VL3 (SEQ ID NO:56)**.

[0013] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein:

- (A) the first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1 (SEQ ID NO:46)**; and

- (B) the first Light Chain Variable Domain comprises the amino acid sequence of:
hCD137 MAB-6 VL3 (SEQ ID NO:56).

[0014] The ~~invention~~disclosure further concerns all the above ~~embodiment~~examples of such **CD137 Binding Molecules**, wherein the molecule is a bispecific molecule comprising a second binding site that immunospecifically binds a **TA**, and wherein the second binding site comprises a second Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a second Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}.

[0015] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the **TA** is selected from the tumor antigens presented in **Tables 1-2**.

[0016] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

- (A) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VLx (SEQ ID NO:63)**; and
- (B) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59)**.

[0017] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein:

- (A) (1) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VL1 (SEQ ID NO:58)**;
or
(2) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72)**;
and
- (B) (1) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH1 (SEQ ID NO:57)**;
(2) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:67)**;
(3) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3 (SEQ ID NO:68)**;
(4) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:69)**;

- (5) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:70)**;
or
- (6) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:71)**.

[0018] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of:

- (A) **hPD-L1 MAB-2 VH1 (SEQ ID NO:57)**;
- (B) **hPD-L1 MAB-2 VH2 (SEQ ID NO:67)**;
- (C) **hPD-L1 MAB-2 VH3 (SEQ ID NO:68)**;
- (D) **hPD-L1 MAB-2 VH4 (SEQ ID NO:69)**;
- (E) **hPD-L1 MAB-2 VH5 (SEQ ID NO:70)**; or
- (F) **hPD-L1 MAB-2 VH6 (SEQ ID NO:71)**.

[0019] The ~~invention~~disclosure further concerns the ~~embodiment~~examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of:

- (A) **hPD-L1 MAB-2 VL1 (SEQ ID NO:58)**; or
- (B) **hPD-L1 MAB-2 VL2 (SEQ ID NO:72)**.

[0020] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the **TA** is 5T4 and wherein:

- (A) (1) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **5T4 MAB-1 VL (SEQ ID NO:93)**; and
(2) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **5T4 MAB-1 VH (SEQ ID NO:92)**; or
- (B) (1) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **5T4 MAB-2 VL (SEQ ID NO:95)**; and
(2) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **5T4 MAB-2 VH (SEQ ID NO:96)**.

[0021] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VH (SEQ ID NO:92)**.

[0022] The ~~invention~~disclosure further concerns the ~~embodiment~~examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VL (SEQ ID NO:93)**.

[0023] The ~~invention~~disclosure further concerns such a **CD137 Binding Molecule**, wherein the **TA** is HER2 and wherein:

- (A) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hHER2-MAB-1 VLx (SEQ ID NO:79)**; and
- (B) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hHER2-MAB-1 VHx (SEQ ID NO:78)**;

[0024] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein:

- (A)
 - (1) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hHER2-MAB-1 VL1 (SEQ ID NO:83)**;
 - (2) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hHER2-MAB-1 VL2 (SEQ ID NO:84)**;
 - or
 - (3) the second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hHER2-MAB-1 VL3 (SEQ ID NO:85)**;and
- (B)
 - (1) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hHER2-MAB-1 VH1 (SEQ ID NO:80)**;
 - (2) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hHER2-MAB-1 VH2 (SEQ ID NO:81)**;
 - or
 - (3) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hHER2-MAB-1 VH3 (SEQ ID NO:82)**.

[0025] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of:

- (A) **hHER2-MAB-1 VHx (SEQ ID NO:78)**;
- (B) **hHER2-MAB-1 VH1 (SEQ ID NO:80)**;
- (C) **hHER2-MAB-1 VH2 (SEQ ID NO:81)**; or
- (D) **hHER2-MAB-1 VH3 (SEQ ID NO:82)**.

[0026] The ~~invention~~disclosure further concerns the ~~embodiment~~examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of:

- (A) **hHER2-MAB-1 VL_x** (SEQ ID NO:79);
- (B) **hHER2-MAB-1 VL1** (SEQ ID NO:83);
- (C) **hHER2-MAB-1 VL2** (SEQ ID NO:84); or
- (D) **hHER2-MAB-1 VL3** (SEQ ID NO:85).

[0027] The ~~invention~~disclosure further concerns all the above ~~embodiment~~examples of such **CD137 Binding Molecules**, wherein the molecule is an antibody, a bispecific tetravalent Fc-bearing diabody, or a bispecific trivalent molecule.

[0028] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the molecule is bispecific and tetravalent, and comprises a first, a second, a third, a fourth, and optionally a fifth polypeptide chain, wherein the polypeptide chains form a covalently bonded complex.

[0029] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the molecule is bispecific and trivalent, and comprises a first, a second, a third, and a fourth, polypeptide chain, wherein the polypeptide chains form a covalently bonded complex.

[0030] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of all such **CD137 Binding Molecules** wherein the molecule comprises an Fc Region of the IgG1, IgG2, IgG3, or IgG4 isotype and optionally wherein the molecule further comprises a Hinge Domain.

[0031] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of all such **CD137 Binding Molecules** wherein the Fc Region is a variant Fc Region that comprises one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR and/or enhances the serum half-life, and more particularly, wherein the modifications comprise at least one amino acid substitution selected from the group consisting of:

- (A) L234A; L235A;
- (B) L234A and L235A;
- (C) M252Y; M252Y and S254T;
- (D) M252Y and T256E;
- (E) M252Y, S254T and T256E; or
- (F) K288D and H435K;

wherein the numbering is that of the EU index as in Kabat.

[0032] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

- (A) the first and third polypeptide chains comprise the amino acid sequence of **SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120**; and
- (B) the second and fourth polypeptide chains comprise the amino acid sequence of **SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, or SEQ ID NO:139**.

[0033] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the molecule comprises:

- (A) **SEQ ID NO:116 and SEQ ID NO:117**;
- (B) **SEQ ID NO:118 and SEQ ID NO:119**;
- (C) **SEQ ID NO:120 and SEQ ID NO:119**;
- (D) **SEQ ID NO:118 and SEQ ID NO:121**;
- (E) **SEQ ID NO:120 and SEQ ID NO:121**;
- (F) **SEQ ID NO:120 and SEQ ID NO:122**;
- (G) **SEQ ID NO:120 and SEQ ID NO:123**;
- (H) **SEQ ID NO:120 and SEQ ID NO:124**;
- (I) **SEQ ID NO:120 and SEQ ID NO:125**;
- (J) **SEQ ID NO:120 and SEQ ID NO:126**; or
- (K) **SEQ ID NO:120 and SEQ ID NO:139**.

[0034] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

- (A) the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:127, SEQ ID NO:133, or SEQ ID NO:135**;
- (B) the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:128, SEQ ID NO:134, or SEQ ID NO:136**;
- (C) the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:129, or SEQ ID NO:131**; and
- (D) the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:130, SEQ ID NO:132**.

[0035] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **CD137 Binding Molecule**, wherein the molecule comprises:

- (A) SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, and SEQ ID NO:130;
- (B) SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:131, and SEQ ID NO:132;
- (C) SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:131, and SEQ ID NO:132; or
- (D) SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:131, and SEQ ID NO:132.

[0036] The ~~invention~~disclosure additionally concerns a pharmaceutical composition comprising any of the above-described **CD137 Binding Molecules**, and a physiologically acceptable carrier.

[0037] The ~~invention~~disclosure additionally concerns the use of such **CD137 Binding Molecules**, or such a pharmaceutical composition, in the treatment of cancer characterized by the expression of the **TA**.

[0037a] In one aspect, the present disclosure refers to a **PD-L1 Binding Molecule**, comprising a Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; wherein:

- (A) said Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VLx (SEQ ID NO:63)**; and
- (B) said Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59)**.

[0038] The ~~invention~~disclosure additionally concerns a **PD-L1 Binding Molecule** that comprises a Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; wherein:

- (A) the Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72)**;
and
- (B)
 - (1) the Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:67)**;
 - (2) the Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3 (SEQ ID NO:68)**
 - (3) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH4 (SEQ ID NO:69)**
 - (4) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH5 (SEQ ID NO:70)**;
or
 - (5) the second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH6 (SEQ ID NO:71)**.

[0039] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **PD-L1 Binding Molecule**, wherein the Heavy Chain Variable Domain comprises the amino acid sequence of:

- (A) **hPD-L1 MAB-2 VH2 (SEQ ID NO:67);**
- (B) **hPD-L1 MAB-2 VH3 (SEQ ID NO:68);**
- (C) **hPD-L1 MAB-2 VH4 (SEQ ID NO:69);**
- (D) **hPD-L1 MAB-2 VH5 (SEQ ID NO:70); or**
- (E) **hPD-L1 MAB-2 VH6 (SEQ ID NO:71).**

[0040] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such a **PD-L1 Binding Molecule**, wherein the Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72).**

[0041] The ~~invention~~disclosure further concerns the ~~embodiment~~example of such **PD-L1 Binding Molecules**, wherein the molecule is an antibody or an antigen binding fragment thereof.

[0042] The ~~invention~~disclosure additionally concerns a pharmaceutical compositions comprising any of the above-described **PD-L1 Binding Molecules**, and a physiologically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the **CD137 Binding Molecule** as disclosed herein or the **PD-L1 Binding Molecule** as disclosed herein, and a physiologically acceptable carrier.

[0042a] In one aspect, the present disclosure refers to the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the preparation of a medicament.

[0043] The ~~invention~~disclosure additionally concerns the use of such **PD-L1 Binding Molecules**, or such pharmaceutical compositions, in the treatment of a disease or condition associated with a suppressed immune system or characterized by the expression of PD-L1.

[0044] The ~~invention~~disclosure further concerns such a use, wherein the condition associated with a suppressed immune system or characterized by the expression of PD-L1 is cancer. In one aspect, the present disclosure refers to the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the treatment of a cancer. In one aspect, the present disclosure refers to use of the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a cancer.

[0045] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of all such uses, wherein the cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

[0046] The ~~invention~~disclosure further concerns a method of enhancing the activity of a tumor targeting agent comprising administering the tumor target agent in combination with any of the above-described **CD137 Binding Molecules**, any of the above-described **PD-L1 Binding Molecules**, or any of the above-described pharmaceutical compositions.

[0047] The ~~invention~~disclosure additionally concerns a method of treating a disease or condition associated with a suppressed immune system or characterized by the expression of a **TA** comprising administering to a subject in need thereof and of the above-described **CD137 Binding Molecules**, any of the above-described **PD-L1 Binding Molecules**, or any of the above-described pharmaceutical compositions.

[0048] The ~~invention~~disclosure further concerns such a method, further comprising administering a tumor targeting agent.

[0049] The ~~invention~~disclosure further concerns such a method, wherein the condition associated with a suppressed immune system or characterized by the expression of the tumor **TA** is cancer.

[0050] The ~~invention~~disclosure further concerns all the above ~~embodiment~~examples of such a method, wherein the tumor target agent is an antibody, an epitope binding fragment of an antibody, or an agent that mediates T-cell redirected killing of a target cell.

[0051] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example such methods, wherein the cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

[0052] ~~In one aspect, the present disclosure refers to~~The ~~invention~~ additionally concerns a nucleic acid encoding the **CD137 Binding Molecule** ~~as disclosed herein~~of any of the above embodiments, or the **PD-L1 Binding Molecule** ~~as disclosed herein~~of any of the above embodiments.

[0053] The ~~invention~~disclosure further concerns an expression vector comprising such nucleic acid.

[0054] The ~~invention~~disclosure additionally concerns a cell comprising a nucleic acid according to any of the above ~~embodiment~~examples or an expression vector of any of the above ~~embodiment~~examples.

[0055] The ~~invention~~disclosure further concerns a such cell, wherein said cell is a mammalian cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0056] **Figure 1A-1D** provides schematics showing representative covalently bonded diabodies comprising Fc Regions. **Figures 1A-1D** show tetravalent diabodies having four epitope-binding sites composed of two pairs of polypeptide chains, (*i.e.*, four polypeptide

WHAT IS CLAIMED IS:

Claim 1. A **CD137 Binding Molecule** comprising a first binding site that immunospecifically binds to an epitope of CD137, wherein said first binding site comprises a first Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a first Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; and wherein:

- (A) said first Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **CD137 MAB-6 VL1 (SEQ ID NO:50)**; and
- (B) said first Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **CD137 MAB-6 VH1 (SEQ ID NO:46)**.

Claim 2. The **CD137 Binding Molecule** of claim 1, wherein:

(A) said first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1 (SEQ ID NO:46)**; and

(B) said first Light Chain Variable Domain comprises the amino acid sequence of:

(1) **hCD137 MAB-6 VL1 (SEQ ID NO:50)**;

(2) **hCD137 MAB-6 VL2 (SEQ ID NO:55)**; or

(3) **hCD137 MAB-6 VL3 (SEQ ID NO:56)**.

~~Claim 3. The **CD137 Binding Molecule** of any one of claims 1-2, wherein said first Light Chain Variable Domain comprises the amino acid sequence of:~~

~~(A) **hCD137 MAB-6 VL1 (SEQ ID NO:54)**;~~

~~(B) **hCD137 MAB-6 VL1 (SEQ ID NO:50)**;~~

~~(B) **hCD137 MAB-6 VL2 (SEQ ID NO:55)**; or~~

~~(C) **hCD137 MAB-6 VL3 (SEQ ID NO:56)**.~~

Claim ~~43~~. The **CD137 Binding Molecule** of claim 1 or claim 2~~any one of claims 1-3~~, wherein:

(A) said first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1 (SEQ ID NO:46)**; and

(B) said first Light Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VL3 (SEQ ID NO:56)**.

Claim ~~54~~. The **CD137 Binding Molecule** of any one of claims 1-~~43~~, ~~wherein said molecule is a bispecific molecule~~ comprising a second binding site that immunospecifically binds to an epitope of PD-L1a tumor antigen (TA), and wherein said second binding site comprises a second Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a second Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; and wherein:

- (A) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hPD-L1 MAB-2 VLx (SEQ ID NO:63); and
- (B) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hPD-L1 MAB-2 VHx (SEQ ID NO:59).

~~Claim 6. The **CD137 Binding Molecule** of claim 5, wherein said TA is selected from the antigens presented in Tables 1-2.~~

~~Claim 7. The **CD137 Binding Molecule** of claim 5, wherein said TA is PD-L1 and wherein:~~

- ~~(A) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hPD-L1 MAB-2 VLx (SEQ ID NO:63); and~~
- ~~(B) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hPD-L1 MAB-2 VHx (SEQ ID NO:59).~~

~~Claim 8. The **CD137 Binding Molecule** of claim 7, wherein:~~

- ~~(A) (1) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hPD-L1 MAB-2 VL1 (SEQ ID NO:58); or~~
- ~~(2) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hPD-L1 MAB-2 VL2 (SEQ ID NO:72);~~

~~and~~

- ~~(B) (1) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH1 (SEQ ID NO:57);**~~
- ~~(2) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:67);**~~
- ~~(3) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3 (SEQ ID NO:68);**~~
- ~~(4) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:69);**~~
- ~~(5) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:70); or**~~
- ~~(6) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:71).**~~

Claim 95. The **CD137 Binding Molecule** of claim 48, wherein:

(A) said second Heavy Chain Variable Domain comprises the amino acid sequence of:

- ~~(A1)~~ **hPD-L1 MAB-2 VH1 (SEQ ID NO:57);**
- ~~(B2)~~ **hPD-L1 MAB-2 VH2 (SEQ ID NO:67);**
- ~~(C3)~~ **hPD-L1 MAB-2 VH3 (SEQ ID NO:68);**
- ~~(D4)~~ **hPD-L1 MAB-2 VH4 (SEQ ID NO:69);**
- ~~(E5)~~ **hPD-L1 MAB-2 VH5 (SEQ ID NO:70); or**
- ~~(F6)~~ **hPD-L1 MAB-2 VH6 (SEQ ID NO:71); and**

(B) said second Light Chain Variable Domain comprises the amino acid sequence of:

- (1) hPD-L1 MAB-2 VL1 (SEQ ID NO:58); or
- (2) hPD-L1 MAB-2 VL2 (SEQ ID NO:72).

Claim 10. ~~The **CD137 Binding Molecule** of any one of claims 8 or 9, wherein said second Light Chain Variable Domain comprises the amino acid sequence of:~~

~~(A) **hPD-L1 MAB-2 VL1 (SEQ ID NO:58); or**~~

~~(B) **hPD-L1 MAB-2 VL2 (SEQ ID NO:72).**~~

Claim 11. ~~The **CD137 Binding Molecule** of claim 5, wherein the **TA** is **5T4** and wherein:~~

~~(A) (1) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **5T4 MAB-1 VL (SEQ ID NO:93); and**~~

~~(2) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **5T4 MAB-1 VH (SEQ ID NO:92); or**~~

~~(B) (1) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **5T4 MAB-2 VL (SEQ ID NO:95); and**~~

~~(2) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **5T4 MAB-2 VH (SEQ ID NO:96).**~~

Claim 12. ~~The **CD137 x TA Binding Molecule** of claim 11, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VH (SEQ ID NO:92).**~~

Claim 13. ~~The **CD137 x TA Binding Molecule** of claim 11 or 12 wherein the second Light Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VL (SEQ ID NO:93).**~~

Claim 6. The **CD137 Binding Molecule** of claim 5, wherein:

(A) said second Heavy Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VH4 (SEQ ID NO:69); and**

(B) said second Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72).**

Claim 147. The **CD137 Binding Molecule** of any one of claims 51-3, comprising a second binding site that immunospecifically binds to an epitope of HER2, wherein said second binding site comprises a second Light Chain Variable Domain that

comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a second Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; wherein the TA is HER2
and wherein:

(A) (1) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hHER2-MAB-1 VL_x (SEQ ID NO:79); and

~~(B)~~ (2) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hHER2-MAB-1 VH_x (SEQ ID NO:78);

or

~~(B)~~ (1) said second Heavy Chain Variable Domain comprises the amino acid sequence of hHER2-MAB-1 VH1 (SEQ ID NO:80); hHER2-MAB-1 VH2 (SEQ ID NO:81); or hHER2-MAB-1 VH3 (SEQ ID NO:82); and

(2) said second Light Chain Variable Domain comprises the amino acid sequence of: hHER2-MAB-1 VL1 (SEQ ID NO:83); hHER2-MAB-1 VL2 (SEQ ID NO:84); or hHER2-MAB-1 VL3 (SEQ ID NO:85);

or

~~(C)~~ said second Heavy Chain Variable Domain comprises the amino acid sequence of hHER2-MAB-1 VH1 (SEQ ID NO:80) and said second Light Chain Variable Domain comprises the amino acid sequence of hHER2-MAB-1 VL3 (SEQ ID NO:85).

~~Claim 15. The CD137 Binding Molecule of claim 14, wherein:~~

~~(A) (1) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hHER2-MAB-1 VL1 (SEQ ID NO:83);~~

~~(2) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hHER2-MAB-1 VL2 (SEQ ID NO:84); or~~

~~(3) said second Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of hHER2-MAB-1 VL3 (SEQ ID NO:85);~~

and

~~(B) — (1) — said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hHER2 MAB-1 VH1 (SEQ ID NO:80);~~

~~(2) — said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hHER2 MAB-1 VH2 (SEQ ID NO:81); or~~

~~(3) — said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hHER2 MAB-1 VH3 (SEQ ID NO:82).~~

~~Claim 16. — The CD137 Binding Molecule of claim 15, wherein said second Heavy Chain Variable Domain comprises the amino acid sequence of:~~

~~(A) — hHER2 MAB-1 VH1 (SEQ ID NO:80);~~

~~(B) — hHER2 MAB-1 VH2 (SEQ ID NO:81); or~~

~~(C) — hHER2 MAB-1 VH3 (SEQ ID NO:82).~~

~~Claim 17. — The CD137 Binding Molecule of any one of claims 15 or 16, wherein said second Light Chain Variable Domain comprises the amino acid sequence of:~~

~~(A) — hHER2 MAB-1 VL1 (SEQ ID NO:83);~~

~~(B) — hHER2 MAB-1 VL2 (SEQ ID NO:84); or~~

~~(C) — hHER2 MAB-1 VL3 (SEQ ID NO:85).~~

Claim ~~188~~. The CD137 Binding Molecule of any one of claims 1-~~177~~, which is an antibody or a bispecific tetravalent Fc-bearing diabody, or a bispecific trivalent molecule.

Claim ~~199~~. The CD137 Binding Molecule of any one of claims 1-~~178~~, wherein said molecule is bispecific and tetravalent, and comprises a first polypeptide chain, a second polypeptide chain, a third polypeptide chain, and a fourth polypeptide chain, wherein said polypeptide chains form a covalently bonded complex.

Claim 10. The CD137 Binding Molecule of claim 9, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:120; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:139; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:120 and

the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:139.

Claim ~~20~~11. The **CD137 Binding Molecule** of any one of claims 1-~~17~~8, wherein said molecule is bispecific and trivalent, and comprises a first polypeptide chain, a second polypeptide chain, a third polypeptide chain, and a fourth, polypeptide chain, wherein said polypeptide chains form a covalently bonded complex.

~~Claim 21. The **CD137 Binding Molecule** of claim 19, wherein said **TA** is PD-L1 and wherein:~~

~~(A) — said first and third polypeptide chains comprise the amino acid sequence of **SEQ ID NO:116**, **SEQ ID NO:118**, or **SEQ ID NO:120**; and~~

~~(B) — said second and fourth polypeptide chains comprise the amino acid sequence of **SEQ ID NO:117**, **SEQ ID NO:119**, **SEQ ID NO:121**, **SEQ ID NO:122**, **SEQ ID NO:123**, **SEQ ID NO:124**, **SEQ ID NO:125**, **SEQ ID NO:126**, or **SEQ ID NO:139**.~~

~~Claim 22. The **CD137 Binding Molecule** of claim 21, wherein said molecule comprises:~~

~~(A) — **SEQ ID NO:116** and **SEQ ID NO:117**;~~

~~(B) — **SEQ ID NO:118** and **SEQ ID NO:119**;~~

~~(C) — **SEQ ID NO:120** and **SEQ ID NO:119**;~~

~~(D) — **SEQ ID NO:118** and **SEQ ID NO:121**;~~

~~(E) — **SEQ ID NO:120** and **SEQ ID NO:121**;~~

~~(F) — **SEQ ID NO:120** and **SEQ ID NO:122**;~~

~~(G) — **SEQ ID NO:120** and **SEQ ID NO:123**;~~

~~(H) — **SEQ ID NO:120** and **SEQ ID NO:124**;~~

~~(I) — **SEQ ID NO:120** and **SEQ ID NO:125**;~~

~~(J) — **SEQ ID NO:120** and **SEQ ID NO:126**; or~~

~~(K) — **SEQ ID NO:120** and **SEQ ID NO:139**.~~

~~Claim 23. The **CD137 Binding Molecule** of claim 20, wherein said **TA** is PD-L1 and wherein:~~

~~(A) — said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:127**, **SEQ ID NO:133**, or **SEQ ID NO:135**;~~

- (B) ~~said second polypeptide chain comprises the amino acid sequence of~~
~~SEQ ID NO:128, SEQ ID NO:134, or SEQ ID NO:136;~~
- (C) ~~said third polypeptide chain comprises the amino acid sequence of~~ **SEQ**
~~ID NO:129, or SEQ ID NO:131; and~~
- (D) ~~said fourth polypeptide chain comprises the amino acid sequence of~~
~~SEQ ID NO:130, SEQ ID NO:132.~~

Claim 12. The **CD137 Binding Molecule** of claim 11, wherein the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:135**; the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:136**; the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:131** and the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:132**.

~~Claim 24.~~ ~~The **CD137 Binding Molecule** of claim 23, wherein said molecule comprises:~~

(A) ~~SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, and SEQ ID~~
~~NO:130;~~

(B) ~~SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:131, and SEQ ID~~
~~NO:132;~~

(C) ~~SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:131, and SEQ ID~~
~~NO:132; or~~

(D) ~~SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:131, and SEQ ID~~
~~NO:132.~~

Claim 13. The **CD137 Binding Molecule** of claim 11, wherein the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:127**; the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:128**; the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:129** and the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:130**.

~~Claim 25.~~ A pharmaceutical composition comprising the ~~**CD137 Binding Molecule**~~ of any one claims 1-24, and a physiologically acceptable carrier.

~~Claim 26.~~ Use of the ~~**CD137 Binding Molecule**~~ of any one of claims 6-24, or the pharmaceutical composition of claim 25, in the treatment of a disease or condition associated with or characterized by the expression of said **TA**.

Claim 14. A **PD-L1 Binding Molecule**, comprising a Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; wherein:

- (A) said Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VLx (SEQ ID NO:63)**; and
- (B) said Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59)**.

Claim 15. The **PD-L1 Binding Molecule** of claim 14, wherein:

- (A) said Heavy Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VH4 (SEQ ID NO:69)**; and
- (B) said Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72)**.

~~Claim 27. A **PD-L1 Binding Molecule** comprising a Light Chain Variable Domain that comprises a CDR_{L1}, CDR_{L2} and CDR_{L3}, and a Heavy Chain Variable Domain that comprises a CDR_{H1}, CDR_{H2} and CDR_{H3}; wherein:~~

- ~~(A) said Light Chain Variable Domain CDR_{L1}, CDR_{L2}, and CDR_{L3} are the Light Chain CDRs of **hPD-L1 MAB-2 VL2 (SEQ ID NO:72)**;~~

~~and~~

- ~~(B) (1) said Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2 (SEQ ID NO:67)**;~~
- ~~(2) said Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3 (SEQ ID NO:68)**~~
- ~~(3) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH4 (SEQ ID NO:69)**~~
- ~~(4) said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH5 (SEQ ID NO:70)**; or~~

(5) ~~—said second Heavy Chain Variable Domain CDR_{H1}, CDR_{H2}, and CDR_{H3} are the Heavy Chain CDRs of hPD-L1 MAB-2 VH6 (SEQ ID NO:71).~~

~~Claim 28. The PD-L1 Binding Molecule of claim 27, wherein said Heavy Chain Variable Domain comprises the amino acid sequence of:~~

- ~~(A) hPD-L1 MAB-2 VH2 (SEQ ID NO:67);~~
- ~~(B) hPD-L1 MAB-2 VH3 (SEQ ID NO:68);~~
- ~~(C) hPD-L1 MAB-2 VH4 (SEQ ID NO:69);~~
- ~~(D) hPD-L1 MAB-2 VH5 (SEQ ID NO:70); or~~
- ~~(E) hPD-L1 MAB-2 VH6 (SEQ ID NO:71).~~

~~Claim 29. The PD-L1 Binding Molecule of any one of claims 27-28, wherein said Light Chain Variable Domain comprises the amino acid sequence of hPD-L1 MAB-2 VL2 (SEQ ID NO:72).~~

~~Claim 30. The PD-L1 Binding Molecule of any one claims 27-29, wherein said molecule is an antibody or an antigen-binding fragment thereof.~~

~~Claim 3116. A pharmaceutical composition comprising the CD137 Binding Molecule of any one of claims 1-13 or the PD-L1 Binding Molecule of claim 14 or claim 15any one claims 27-30, and a physiologically acceptable carrier.~~

~~Claim 17. The CD137 Binding Molecule of any one of claims 1-13, the PD-L1 Binding Molecule of claim 14 or claim 15, or the pharmaceutical composition of claim 16, for use in the preparation of a medicament.~~

~~Claim 18. The CD137 Binding Molecule of any one of claims 1-13, the PD-L1 Binding Molecule of claim 14 or claim 15, or the pharmaceutical composition of claim 16, for use in the treatment of a cancer.~~

~~Claim 3219. Use of the CD137 Binding Molecule of any one of claims 1-13, the PD-L1 Binding Molecule of claim 14 or claim 15any one of claims 27-30, or the pharmaceutical composition of claim 1631, in the manufacture of a medicament for the treatment of a cancer-disease or condition associated with a suppressed immune system or characterized by the expression of PD-L1.~~

~~Claim 33. The use of claim 32, wherein said disease or condition associated with a suppressed immune system or characterized by the expression of PD-L1 is cancer.~~

Claim ~~34~~20. The **CD137 Binding Molecule, the PD-L1 Binding Molecule or the pharmaceutical composition for use of claim 18, or the use of claim 19**~~any one of claims 26, or 33~~, wherein said cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

~~Claim 35. A method of enhancing the activity of a tumor targeting agent comprising administering said tumor target agent in combination with the **CD137 Binding Molecule** of any one of claims 1-24, the **PD-L1 Binding Molecule** of any one of claims 27-30, or the pharmaceutical composition of any one of claims 25 or 31.~~
~~Claim 36. A method of treating a disease or condition associated with a suppressed immune system or characterized by the expression of a **TA** comprising administering to a subject in need thereof of the **CD137 Binding Molecule** of any one of claims 1-24, the **PD-L1 Binding Molecule** of any one of claims 27-30, or the pharmaceutical composition of claim 25 or 31.~~

~~Claim 37. The method of claim 36, wherein the condition associated with a suppressed immune system or characterized by the expression of the **TA** is cancer.~~

~~Claim 38. The method of claim 36 or 37, further comprising administering a tumor targeting agent.~~

~~Claim 39. The method of claim 35 or 38, wherein said tumor target agent is an antibody, an epitope binding fragment of an antibody, or an agent that mediates T-cell redirected killing of a target cell.~~

~~Claim 40. The method of any one of claims 36-38, wherein the cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.~~

Claim ~~41~~21. A nucleic acid encoding the **CD137 Binding Molecule** of any one of claims 1-~~24~~13, or the **PD-L1 Binding Molecule** of claim 14 or claim 15~~any one of claims 27-30~~.

~~Claim 42. An expression vector comprising a nucleic acid according to claim 41.~~

~~Claim 43. A cell comprising a nucleic acid according to claim 41 or an expression vector according to claim 42.~~

~~Claim 44. The cell according to claim 43, wherein said cell is a mammalian cell.~~